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10/560,280	04/26/2006	Takeshi Tabira	2007_0585	3468

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
01/28/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,280	TABIRA ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-41* is/are pending in the application.

4a) Of the above claim(s) *34-37,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-33,38 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/02/2010 has been entered.

This application 10/560,280 is a 371 of PCT/JP04/08224 06/11/2004 and claims benefit of foreign applications JAPAN 2003-169714 06/13/2003, JAPAN 2003-371103 filed on 10/30/2003.

Claims 1-29 are cancelled. Claims 30-41 are newly added, which correspond to claims 19-29 filed on 09/01/2009. However, newly added independent claim 30 recites the limitation "whereby the concentration of TGF-β in the blood of the subject is reduced" that is not recited in the independent claim 29 filed on 09/01/2009. On the other had, the limitation "which expresses β-amyloid peptide in intestinal cells" recited in independent claim 29 field on 09/01/2009 is currently recited in new dependent claim 31 filed on 08/02/2010.

For the clarity of record and to accommodate newly added claims 30-41 filed on 08/02/2010, the newly added claims 30-41 filed on 08/02/2010, which correspond to claims 19-29 filed on 09/01/2009, are assigned to the revised Groups I-IV listed below in this office action. It is noted that Applicant's election of Group I in the reply filed on 11/10/2009 remains for the requested continuation of examination of instant application.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 30-33, 38, and 41, drawn to a method for treating Alzheimer's disease, comprising administering an adeno-associated virus vector in a therapeutically effective amount to a subject whereby the concentration of TGF-β in the blood of the subject is reduced, wherein the adeno-associated virus vector comprises DNA encoding a β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form, wherein said β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2, and wherein the DNA encoding said β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1.

II. Claims 30, 31, 34, 35, 38, and 41, drawn to a method for treating Alzheimer's disease, comprising administering an adeno-associated virus vector in a therapeutically effective amount to a subject whereby the concentration of TGF-β in the blood of the subject is reduced, wherein the adeno-associated virus vector comprises DNA encoding a β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form, wherein said β-amyloid peptide comprises the amino acid sequence as shown in SEQ ID NO: 2, and wherein the DNA encoding said β-amyloid peptide comprises the nucleotide sequence as shown in SEQ ID NO: 1.

III. Claims 30, 31, 36-38 and 41, drawn to a method for treating Alzheimer's disease, comprising administering an adeno-associated virus vector in a therapeutically effective amount to a subject whereby the concentration of TGF-β in the blood of the subject is reduced, wherein the adeno-associated virus vector comprises DNA encoding a β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form, wherein said β-amyloid peptide comprises the amino acid sequence as shown in SEQ ID NO: 4, and wherein the DNA encoding said β-amyloid peptide comprises the nucleotide sequence as shown in SEQ ID NO: 3.

IV. Claims 30, 31 and 38-41, drawn to a method for treating Alzheimer's disease, comprising administering an adeno-associated virus vector in a therapeutically effective amount to a subject whereby the concentration of TGF-β in the blood of the subject is reduced, wherein the adeno-associated virus vector comprises DNA encoding a β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form, wherein said signal peptide comprises the amino acid sequence as shown in SEQ ID NO: 6, and wherein the DNA encoding said signal peptide comprises the nucleotide sequence as shown in SEQ ID NO: 5.

Claims 30-41 are pending. Claims 34-37, 39, and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 30-33, 38, and 41 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Previous rejection of claims 19-21 and 29 under 35 U.S.C. 103(a) as being unpatentable over **Huston et al** (US 2005/0255113, publication date 11/17/2005, filed on 09/27/2004, continuation of 09/620,955 filed on 07/21/2000, provisional application 60/146,047, filed on 07/27/1999), issued on 10/14/2003, filed on 08/21/2000) in view of **Kuwako et al.** (Kuwako et al., Activation of calpain in cultured neurons overexpressing Alzheimer amyloid precursor protein, Brain Res Mol Brain Res. 107(2):166-75, 2002), **Milton et al.** (WO 2002/36614), and **Findeis et al.** (US patent 5,854,204, issued on 12/29/1998) is **moot** because the claims have been cancelled.

The following new 103(a) rejection is necessitated by claim amendments filed on 08/02/2010.

4. Claims 30-33, 38, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Huston et al.** (US 2005/0255113, publication date 11/17/2005, filed on 09/27/2004, continuation of 09/620,955 filed on 07/21/2000, provisional application 60/146,047, filed on 07/27/1999), issued on 10/14/2003, filed on 08/21/2000) in view of **Kuwako et al.** (Kuwako et al., Activation of calpain in cultured neurons overexpressing Alzheimer amyloid precursor protein, Brain Res Mol Brain Res. 107(2):166-75, 2002), **Wyss-Coray et al.** (Wyss-Coray et al., TGF-β1 promotes

microglial amyloid-β clearance and reduces plaque burden in transgenic mice, Nat. Med. 7(5):612-8, 2001), **Milton et al.** (WO 2002/36614), and **Findeis et al.** (US patent 5,854,204, issued on 12/29/1998).

Claim 30 is directed to a method for treating Alzheimer's disease, comprising administering an adeno-associated virus vector in a therapeutically effective amount to a subject whereby the concentration of TGF-β in the blood of the subject is reduced, wherein the adeno-associated virus vector comprises DNA encoding a β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form.

Claim 31 is directed to the method according to claim 30, wherein the β-amyloid peptide is expressed in intestinal cells by the adeno-associated virus vector.

Claim 32 is directed to the method according to claim 30, wherein said b-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2.

Claim 33 is directed to the method according to claim 30, wherein the DNA encoding said β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1.

Claim 38 is directed to the method according to claim 30, wherein said signal peptide is a signal peptide of amyloid precursor protein.

Claim 41 is directed to the method according to claims 30, said administering is orally administering.

Claim interpretation: The limitation "wherein said signal peptide is a signal peptide of amyloid precursor protein" recite din claim 33 reads on the signal peptide located in the wild type N-terminal of amyloid precursor protein (APP). This interpretation is based on the disclosure in paragraph [0028] of specification, US 2009/0004144, publication of instant application.

Huston et al. teaches a method for inhibiting the formation of intracellular aggregates of a selected polypeptide associated with neurological disorders in an animal by immunizing the

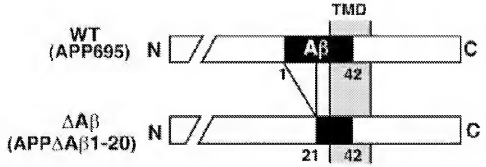
animal, including a human patient, with an immunogen having an epitope in common with the selected polypeptide, where the immunizing provokes a host antibody immune response sufficient for inhibiting the formation of aggregates, e.g., intracellular aggregates of the selected polypeptide from occurring. In a preferred embodiment, the immunogen is an expressible nucleic acid vaccine, e.g., a DNA vaccine, encoding a polypeptide comprising an epitope in common with a polypeptide such as, e.g., Amyloid Precursor Protein (See abstract and paragraph [0023], Huston et al. US 2005/0255113).

With regard to adeno-associated virus (AAV), Huston et al teaches expression vectors, such as viral vectors including adenoviruses and adeno-associated viruses), which serve equivalent functions (See paragraph [0125], Huston et al. US 2005/0255113).

With regard to orally administering AAV expressing β-amyloid peptide in intestinal cells recited in claim 31 and 41, Huston et al. teaches that the term "administering" refers to dispensing, delivering or applying the therapeutic agent to an animal or human by any suitable route for delivery of the therapeutic agent to the desired location in the animal or human, including delivery by either the parenteral or oral route, intramuscular injection, subcutaneous (intradermal) injection, intravenous injection, buccal administration, transdermal delivery, intracranial delivery, and administration by the intranasal or respiratory tract route. Huston et al teaches that the term "administering" is further intended to refer to bringing the therapeutic agent into close proximity with a cell, such that the therapeutic agent can exert its effects on the cell (See paragraph [0082], Huston et al. US 2005/0255113). It is prima facie obvious that intestinal cells are targeted by the AAV vector recited in claim 31 of instant application upon oral administration of adeno-associated viruses (AAV) vector taught by Huston et al.

Huston et al. does not explicitly teaches **(i)** the limitation "DNA encoding a β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form" recited in claim 30 of instant application, **(ii)** the limitation "the concentration of TGF-β in the blood of the subject is reduced" recited in claim 30, **(iii)** DNA encoding said β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, recited in claim 33 of instant application, and **(iv)** the limitation β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2 recited in claim 32 of instant application.

(i) With regard to the limitation "DNA encoding a β-amyloid peptide and DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide, in an operative form" recited in claim 30, **Kuwako et al.** teaches that Alzheimer's disease (AD) is a neurodegenerative disease and studies of the molecular mechanism of AD indicates that overexpression of wild-type amyloid precursor protein (APP) in postmitotic neurons induces cleavage-dependent activation of caspase-3 both in vivo and in vitro by recombinant adenovirus, which is an obvious variant of adeno-associated virus, expressing wild-type APP and its Aβ (1-20) lacking mutant (APPΔAβ20) (See abstract and material and Methods, Figure 1A, shown below, Kuwako et al., Activation of calpain in cultured neurons overexpressing Alzheimer amyloid precursor protein, Brain Res Mol Brain Res. 107(2):166-75, 2002).



It is noted that the limitation "DNA encoding a signal peptide capable of extracellularly secreting said β-amyloid peptide" reads on the signal peptide located in the wild type N-terminal of amyloid precursor protein (APP).

(ii) With regard to the limitation "the concentration of TGF-β in the blood of the subject is reduced" recited in claim 30, **Wyss-Coray et al.** teaches TGF-β1 promotes microglial amyloid-beta clearance and reduces plaque burden in transgenic mice. Wyss-Coray et al. teaches that abnormal accumulation of the amyloid-β peptide (Aβ) in the brain appears crucial to pathogenesis in all forms of Alzheimer disease (AD). Transforming growth factor β1 (TGF- β1), a key regulator of the brain's responses to injury and inflammation, has been implicated in Aβ deposition in vivo. Wyss-Coray et al. demonstrate that in human cases of AD, Aβ immunoreactivity associated with parenchymal plaques was inversely correlated with Aβ in blood vessels and cortical TGF-β1 mRNA levels. The reduction of parenchymal plaques in hAPP/TGF-β1 mice was associated with a strong activation of microglia and an increase in inflammatory mediators. Recombinant TGF-β1 stimulated Aβ clearance in microglial cell cultures. These results demonstrate that TGF-β1 is an important modifier of amyloid deposition in vivo and indicate that TGF-β1 might promote microglial processes that inhibit the

accumulation of Aβ in the brain parenchyma (See abstract, Wyss-Coray et al., TGF-β1 promotes microglial amyloid-beta clearance and reduces plaque burden in transgenic mice, Nat. Med. 7(5):612-8, 2001).

It is noted that the administration of AAV expressing β-amyloid peptide in a subject, by the combined teachings of Huston et al. and Kuwako et al., increases the Aβ immunoreactivity in the subject, which is inversely correlated with Aβ in blood vessels and cortical TGF-β1 mRNA levels, by the teachings of Wyss-Coray et al. Accordingly, it is prima facie obvious that decreased TGF-β1 mRNA levels is associated with "the concentration of TGF-β in the blood of the subject is reduced" recited in claim 30 of instant application.

(iii) With regard to DNA encoding said β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1 recited in claim 33 of instant application, **Milton et al.** teaches amyloid-beta (Aβ) 1-43, its fragment capable of binding to the Aβ protein within the Aβ 1-43 region. The sequence alignment of the sequences of SEQ ID No: 1 with the sequences taught by Milton et al. is provided below, with bold sequences indicating nucleotide sequences 10-30 of SEQ ID NO: 1.

SEQ ID No: 1

```
RESULT 1
ABK52998
ID   ABK52998 standard; cDNA; 129 BP.
XX
AC   ABK52998;
XX
DT   21-AUG-2002  (first entry)
XX
DE   Human cDNA encoding amyloid beta peptide 1-43.
XX
KW   Human; ss; amyloid beta 1-43; Alzheimer's disease; antisense peptide;
KW   cyclin dependent kinase; nootropic; Abeta; phosphorylation; vaccine;
KW   neuroprotective; catalase; p34-cdc22.
```

```
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   CDS             1. .129
FT                   /*tag=  a
FT                   /product= "Amyloid beta 1-43"
FT                   /partial
FT                   /note= "No start or stop codon shown"
XX
PN   WO200236614-A2.
XX
PD   10-MAY-2002.
XX
PF   01-NOV-2001; 2001WO-GB004843.
XX
PR   01-NOV-2000; 2000GB-00026738.
PR   01-NOV-2000; 2000GB-00026739.
XX
PA   (INSI-) INSIGHT BIOTECHNOLOGY LTD.
XX
PI   Milton NGN;
XX
DR   WPI; 2002-490001/52.
DR   P-PSDB; AAU98701.
XX
PT   New antisense peptides of amyloid beta protein residues 1-32, useful for
PT   detecting, preventing and treating Alzheimer's disease, or for
PT   identifying therapeutic agents that prevent cytotoxicity or
PT   phosphorylation of amyloid beta.
XX
PS   Disclosure; Fig 1; 44pp; English.
XX
CC   The invention relates to a peptide (I) comprising the antisense sequence
CC   of amyloid-beta (Abeta) 1-43, its fragment capable of binding to the
CC   Abeta protein within the Abeta 1-43 region, or a homologue of the peptide
CC   or fragment having the same hydropathic profile or at least 60% sequence
CC   identity. Also included are (1) a phosphorylated Abeta protein or its
CC   fragment for use in therapy; (2) an isolated recombinant vector
CC   comprising a polynucleotide encoding (I); (3) an antibody raised against
CC   (I) (including an antibody having no or reduced affinity for the non-
CC   phosphorylated form of the protein and an antibody raised against the
CC   peptides appearing as AAU98708-AAU98716); (5) determining if a patient is
CC   at risk for Alzheimer's disease by analysing a sample from the patient
CC   that contains Abeta to determine if Abeta is phosphorylated, where
CC   phosphorylation indicates a risk of Alzheimer's disease; (6) an assay for
CC   identifying an agent that inhibits the interaction of Abeta protein with
CC   other protein by contacting Abeta protein or its fragment with a target
CC   agent and a peptide that binds to Abeta (or fragment), and determining if
CC   the agent inhibits the peptide from binding to Abeta compared to a
CC   control assay carried out in the absence of the peptide; (7) an assay for
CC   identifying an agent that binds to Abeta within the region Abeta 1-43, by
CC   contacting a target agent with a peptide as defined above, and
CC   determining if the agent binds to the peptide; and (10) a compound that
CC   blocks the activity of a phosphorylated Abeta protein. The antisense
CC   peptide is useful in therapy, and in the manufacture of a medicament for
CC   therapy of a condition mediated by phosphorylation of Abeta or by binding
CC   of endogenous Abeta to catalase, where such condition is Alzheimer's
CC   disease. The peptide comprising the amino acid sequence Abeta 1-43 or its
CC   fragment capable of binding to cyclin-dependent kinase is useful in the
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CC   manufacture of a medicament for therapy of a condition mediated by
CC   phosphorylation of Abeta. The protein kinase inhibitor may be used in the
CC   manufacture of a medicament for treating Alzheimer's disease, where the
CC   inhibitor selectively binds to where protein and the kinase is p34-cdc22.
CC   The antisense peptides may also be used for detecting, preventing and
CC   treating Alzheimer's disease, for identifying therapeutic agents that
CC   prevent Abeta cytotoxicity or phosphorylation of Abeta, and in vaccines.
CC   A phosphorylated Abeta fragment may be used to generate antibodies
CC   specific for the phosphorylated form, or as an antigen in a vaccine
CC   composition. The present sequence encodes Abeta 1-43
XX
SQ   Sequence 129 BP; 38 A; 21 C; 35 G; 35 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 129;  DB 1;  Length 129;
  Best Local Similarity   100.0%;
  Matches  129;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GATGCAGAATTCCGACATGACTCAGGATATGAAGTTCATCATCAAAAATTGGTGTTCTTT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GATGCAGAATTCCGACATGACTCAGGATATGAAGTTCATCATCAAAAATTGGTGTTCTTT 60

Qy         61 GCAGAAGATGTGGGTTCAAACAAAGGTGCAATCATTGGACTCATGGTGGGCGGTGTTGTC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GCAGAAGATGTGGGTTCAAACAAAGGTGCAATCATTGGACTCATGGTGGGCGGTGTTGTC 120

Qy        121 ATAGCGACA 129
              |||||||||
Db        121 ATAGCGACA 129
```

(iv) With regard to the limitation β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2 recited in claim 32 of instant application, **Findeis et al.** teaches β-amyloid peptide (βAP) derivatives, and the βAP derivatives inhibit aggregation of amyloidogenic proteins. The sequence alignment of the sequences of SEQ ID No: 2 with the sequences taught by Findeis et al. are provided below, with bold sequences indicating amino acids 4 to 10 of SEQ ID NO: 2.

SEQ ID No: 2

```
RESULT 14
AAW89362
ID   AAW89362 standard; peptide; 43 AA.
XX
AC   AAW89362;
XX
DT   02-MAR-1999  (first entry)
XX
```

DE Beta-amyloid peptide derivative A-beta-1-43.
XX
KW Human; beta-amyloid peptide; Alzheimer's disease; amyloidogenic protein;
KW aggregation; neurotoxicity; amyloidosis; Down's syndrome; cardiomyopathy;
KW familial amyloid polyneuropathy; bovine spongiform encephalopathy;
KW Creutzfeldt-Jakob disease; bAP.
XX
OS Homo sapiens.
OS Synthetic.
XX
PN US**5854204**-A.
XX
PD 29-DEC-1998.
XX
PF 14-MAR-1996; 96US-00612785.
XX
PR 14-MAR-1995; 95US-00404831.
PR 07-JUN-1995; 95US-00475579.
PR 27-OCT-1995; 95US-00548998.
XX
PA (PRAE-) PRAECIS PHARM INC.
XX
PI Hundal A, Gefter ML, Kasman L, Musso G, Molineaux S, Benjamin H;
PI **Findeis** MA, Chin J, Lee J, Kelley M, Reed M, Wakefield J;
PI Garnick MB, Kubasek W, Signer ER;
XX
DR WPI; 1999-094964/08.
XX
PT New peptide(s) derived from beta-amyloid peptide that inhibit amyloid
PT aggregation - and neurotoxicity, specifically for treatment and
PT prevention of Alzheimer's disease.
XX
PS Example 1; Col 46; 52pp; English.
XX
CC The present invention describes beta-amyloid peptide (bAP) derivatives.
CC The bAP derivatives inhibit aggregation of amyloidogenic proteins and
CC peptides, specifically bAP, and their neurotoxicity, so are useful for
CC treating and preventing any disease involving amyloidosis, specifically
CC Alzheimer's disease but also Down's syndrome, familial amyloid
CC polyneuropathy or cardiomyopathy, bovine spongiform encephalopathy and
CC Creutzfeldt-Jakob disease. The bAP derivatives are also used to diagnose
CC these diseases, in vitro or in vivo, by detecting binding of bAP to
CC labelled bAP derivatives. Some bAP derivatives inhibit bAP aggregation
CC even when bAP is present in molar excess. The present sequence represents
CC a bAP derivative
XX
SQ Sequence 43 AA;

Query Match 100.0%; Score 222; DB 1; Length 43;
Best Local Similarity 100.0%;
Matches 43; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 DAE**FRHDSGY**EVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT 43
||||||||||||||||||||||||||||||||||||||||||
Db 1 DAE**FRHDSGY**EVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT 43

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Huston et al. regarding a method for inhibiting the formation of intracellular aggregates of a selected polypeptide associated with neurological disorders in an animal by immunizing the animal, including a human patient, with an immunogen having an epitope in common with the selected polypeptide, where the immunizing provokes a host antibody immune response sufficient for inhibiting the formation of aggregates, e.g., intracellular aggregates of the selected polypeptide from occurring, wherein the immunogen is an expressible nucleic acid vaccine, e.g., a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), via oral administration of AAV vector to intestinal cells, with the teachings of **(i)** Wyss-Coray et al. regarding in human Aβ immunoreactivity associated with parenchymal plaques was inversely correlated with Aβ in blood vessels and cortical TGF-β1 mRNA levels, **(ii)** Kuwako et al. regarding Alzheimer's disease (AD) is a neurodegenerative disease and studies of the molecular mechanism of AD indicates that overexpression of wild-type amyloid precursor protein (APP) in postmitotic neurons induces cleavage-dependent activation of caspase-3 both in vivo and in vitro by recombinant adenovirus, which is an obvious variant of adeno-associated virus, expressing wild-type APP and its Aβ (1-20) lacking mutant (APPΔAβ20), **(iii)** Milton et al. regarding amyloid-β (Aβ) 1-43, its fragment capable of binding to the Aβ protein within the Aβ 1-43 region, and β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and **(iv)** Findeis et al. regarding β-amyloid peptide (βAP) derivatives, and the βAP derivatives inhibit aggregation of amyloidogenic proteins, and the amino acid sequence

alignment of SEQ ID No: 2 with the sequences taught by Findeis et al., to arrive at the claimed methods recited in claims 30-33, 38, and 41 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Huston et al. with the teachings of Wyss-Coray et al. Kuwako et al., Milton et al., and Findeis et al. because **(i)** Huston et al. teaches that the immunization of a subject with a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of a polypeptide comprising an epitope of amyloid precursor protein (APP), **(ii)** Wyss-Coray et al. teaches in human Aβ immunoreactivity associated with parenchymal plaques was inversely correlated with Aβ in blood vessels and cortical TGF-β1 mRNA levels, **(iii)** Kuwako et al. teaches construction of adenovirus vectors expressing wild-type APP and APPΔAβ20 for analysis of molecular events linked to Alzheimer's disease, **(iv)** Milton et al. teaches β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and (iv) Findeis et al. teaches β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2.

There would have been a reasonable expectation of success given (i) the disclosure of the immunization of a subject with a DNA vaccine, encoding a polypeptide comprising an epitope of amyloid precursor protein (APP), provokes a host antibody immune response sufficient for inhibiting the formation of intracellular aggregates of a polypeptide associated with neurological disorders comprising an epitope of amyloid precursor protein (APP), and the in vivo demonstration of a nucleic acid vaccine for eliciting a therapeutic host antibody immune response against undesired pathogenic intracellular huntingtin polypeptide complexes, by the

teachings of Huston et al. (See Example 8, Huston et al.), (ii) the successful demonstration of the construction of adenovirus vectors expressing wild-type APP and APPΔAβ20 for analysis of molecular events linked to Alzheimer's disease, by the teachings of Kuwako et al., (iii) inverse correlation between Aβ deposits in blood vessels and plaques and association with TGF-β1 expression levels in brains from mice and AD cases, by the teachings of Wyss-Coray et al. (See Figure 4, page 615, Wyss-Coray et al., 2001), and (iv) the disclosure at nucleotide and amino acid levels regarding β-amyloid peptide comprises the nucleotides 10 to 30 of the nucleotide sequence as shown in SEQ ID NO: 1, and β-amyloid peptide comprises the amino acids 4 to 10 of the amino acid sequence as shown in SEQ ID NO: 2, by the teachings of Milton et al. and Findeis et al.

Thus, the claimed invention as a whole was clearly prima facie obvious.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc. that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and KSR Guidelines Update has been published in the Federal Register at 75 Fed. Reg. 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in KSR International Co. v. Teleflex, Inc., the suggestion and motivation to combine the teachings of Huston et al., Kuwako et al., Wyss-Coray et al., Milton et al., and Findeis has been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant's arguments and **Response to Applica*nt's arguments***

Applicant's remarks filed on 08/02/2010 regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above.

It is noted that Wyss-Coray et al. (2001) is cited in the new 103(a) rejection to address the limitation "whereby the concentration of TGF-β in the blood of the subject is reduced" recited in newly added claim 30.

Conclusion

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Primary Examiner
Art Unit 1632